

# HR 756—a new cephalosporin in the treatment of gonorrhoea caused by ordinary and penicillinase-producing strains of *Neisseria gonorrhoeae*

V S RAJAN,\* E H SNG,† ROGER PANG,\* N J TAN,\* T THIRUMOORTHY,\* AND K L YEO†

From the \*Middle Road Hospital, and the †Department of Pathology, Singapore General Hospital, Singapore

**SUMMARY** HR 756, a new cephalosporin, was used in single intramuscular doses of 500 mg to treat 108 men and women with gonorrhoea caused by penicillinase-producing *Neisseria gonorrhoeae* (PPNG) and non-PPNG. Of 102 patients followed up, 99 (97·05%) were cured. Cure rates for PPNG infections and non-PPNG infections were 98·18% and 95·74% respectively. Few adverse side effects were recorded but possible cross-sensitisation with penicillin was observed. Clinical and laboratory antibiotic susceptibility results correlated well. It is concluded that this drug is safe and effective in treating both PPNG and non-PPNG infections.

## Introduction

Gonococci are developing partial and total resistance to penicillin. In late 1975,  $\beta$ -lactamase-producing, or penicillinase-producing, *Neisseria gonorrhoeae* (PPNG) emerged and in the following years quickly found a foothold in certain African and Asian countries. There is thus a need to search for effective alternatives to penicillin in combating these gonococci. None of the alternative drugs listed by the World Health Organisation have the same advantages as penicillin, since some are costly, others toxic, or they may need to be given in multiple doses.<sup>1</sup> The cephalosporins were recognised early to have potential in treating gonorrhoea. However, they and their analogues gave poor treatment results.<sup>2-4</sup> Changes in the chemical structure of the cephalosporins have resulted in an increased antibacterial spectrum, more useful pharmacokinetic properties, and, in some cases, a high level of resistance to  $\beta$ -lactamase hydrolysis.

A second generation cephalosporin, HR 756, 7-2-(2-amino-4-thiazolyl)-2-(Z)-(methoximino)acetamidocephalosporanic acid (figure) has been found to have great  $\beta$ -lactamase stability.<sup>5</sup> We have carried out a study to determine the efficacy of HR 756 in the treatment of gonorrhoea caused by the PPNG and non-PPNG strains. The drug used was

cefotaxime, a water-soluble sodium salt form of HR 756. The clinical response was correlated with antibiotic susceptibility determined in the laboratory.

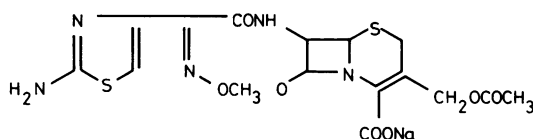


FIG HR 756, 7-2-(2-amino-4-thiazolyl)-2-(Z)-(methoximino)acetamidocephalosporanic acid

## Patients and methods

### STUDY POPULATION

Each patient was given a single intramuscular injection of HR 756 together with probenecid 1 g orally. The following groups of patients were studied: **Group A.** This consisted of male and female prostitutes who came to the hospital for regular check-up. Treatment was given to women with positive results to cervical or rectal cultures of PPNG strains only whereas all men with positive rectal results (PPNG and non-PPNG) were treated. **Group B.** This consisted of other patients (male and female) who attended the hospital. Treatment was given to those with positive results to urethral, cervical, or rectal smears (showing intracellular Gram-negative diplococci). Specimens were taken at the same time for culture for *N gonorrhoeae*. Only those treated patients with confirmed positive culture results were included in the study.

Address for reprints: Dr V S Rajan, Middle Road Hospital, Singapore 7, Republic of Singapore

Received for publication 21 November 1979

# PRETREATMENT INVESTIGATIONS

Before treatment, the following information was recorded: presence of other sexually transmitted diseases, concomitant medication during the period of study, and the body weight of the patient. The following blood tests were also performed: total white and differential counts, platelet counts, blood SGPT, and urea. These were performed because the drug manufacturer reported a low percentage (0.3-0.9%) of leucopenia, thrombocytopenia, eosinophilia, and elevated blood SGPT and urea in some patients given HR 756 for other conditions. The blood tests were repeated on the seventh and fourteenth day after treatment.

# TESTS-OF-CURE

Tests of cure were determined by cultures carried out on the third, seventh, and fourteenth day.

Patients in group B were considered to be cured of the infection when follow-up cultures gave negative results. Treatment failure was diagnosed when one of the cultures gave a positive result and the possibility of reinfection was excluded. Patients in group A usually did not refrain from sexual activities for more than three days. The criteria for cure in this group were therefore modified. A patient was considered cured if cultures continued to give negative results for one week after treatment. When cultures gave positive results on the seventh or fourteenth day, reinfection was diagnosed if patients had resumed sexual activities, otherwise they were considered to be treatment failures.

For cultures, all swabs were inoculated directly on to modified Thayer-Martin medium and incubated at 35°C for 24-48 hours in CO<sub>2</sub> canisters.<sup>6</sup> Identification was by colonial morphology, oxidase test, Gram staining and sugar utilisation. All cultures giving positive results were tested routinely for the presence of penicillinase by the disc diffusion technique using a penicillin disc (10 IU) and confirmed by the rapid iodometric method.<sup>7</sup>

# ANTIBIOTIC SUSCEPTIBILITY

Antibiotic susceptibility was determined routinely in isolates giving positive results. The minimum inhibitory concentrations (MICs) of HR 756 and penicillin G were determined by the agar plate dilution method. Two-fold concentrations of HR 756 from 0.00025 to 0.03 µg/ml and penicillin G from 0.016 to 4 µg/ml were distributed into GC agar base (Difco) supplemented with haemoglobin and IsoVitalex. The test organisms were grown on chocolate agar and then suspended in Mueller-Hinton broth. The suspension turbidity was adjusted to correspond to 0.5 McFarland standard barium sulphate. The suspension was further diluted 1/100, and 10 µl of each suspension was inoculated on to the

antibiotic-containing medium using a multi-point inoculator. The plates were incubated in CO<sub>2</sub> canisters at 35°C overnight. The MIC was determined as the lowest concentration of antibiotic that permitted the growth of no more than one colony.

# STATISTICAL ANALYSIS

Student's *t* test was used to determine the significance of the difference between the mean MICs of PPNG and non-PPNG strains. For the correlation between the MICs of HR 756 and penicillin the product moment method was used.

# Results

One hundred and eight patients with bacteriologically confirmed gonorrhoea were treated with HR 756. Of these infections, 57 were due to PPNG and 51 to non-PPNG (table I).

TABLE I Number of PPNG and non-PPNG infections in patients studied

	Group A	Group B	Total
PPNG	44	13	57
Non-PPNG	10	41	51
Total	54	54	108

# FOLLOW UP

Details of follow-up attendances of patients after treatment are shown in table II.

# TREATMENT RESPONSE

Of 102 patients followed up, 99 (97.05%) were cured and three (2.94%) failed to respond to treatment (table III). Of the 55 patients with PPNG infections who attended for follow up, 54 (98.18%) were cured. Similarly, 45 (95.74%) out of 47 patients with non-PPNG infections responded to treatment. Note that all 11 male prostitutes with positive rectal culture results were cured of their infections. There were four reinfections in group A and none in group B.

# ANTIBIOTIC SUSCEPTIBILITY

Sixty-eight strains were tested for their antibiotic susceptibilities. All the strains were susceptible to 0.03 µg/ml of HR 756 (table IV). The mean MICs for PPNG and non-PPNG strains were 0.11 and 0.0045 µg/ml respectively. This difference is statistically significant ( $t=3.3140$ ;  $P<0.01$ ).

TABLE II Follow up of patients after treatment

Attendance after treatment	Group A	Group B	Total
On 3rd and 7th day	0	9	9
On 3rd, 7th and 14th day	53	40	93
Defaulted	1	5	6
Total	54	54	108

TABLE III Results of treatment

Results of treatment	Strains	Group A		Group B		Total (%)
		M	F	M	F	
Success	PPNG	3	39	10	2	54 } 99 (97.05)
	Non-PPNG	8	2	35	0	
Failure	PPNG	0	1	0	0	1 } 3 (2.94)
	Non-PPNG	0	0	2	0	
Defaulted	PPNG	0	1	1	0	2 } 6
	Non-PPNG	0	0	4	0	

All the PPNG strains grew in the presence of 4 µg/ml of penicillin G. The mean MIC of penicillin G for the non-PPNG strains was 0.5 µg/ml. This is higher than the amount of HR 756 needed to inhibit either PPNG or non-PPNG strains. The concentration of HR 756 needed to inhibit non-PPNG strains was directly related to the MIC of penicillin G for these strains (table V). The correlation is statistically significant ( $t = 6.6156$ ;  $P < 0.001$ ).

The MICs of HR 756 for strains from the three patients who failed to respond to treatment were 0.016, 0.008, and 0.008 µg/ml. When these are compared with those for the other strains tested, the treatment failure rates with different MICs may be found (table VI); treatment failure is apparent when the MIC is 0.008 µg/ml or above.

#### DRUG TOLERANCE

**Pain at injection site.** Two patients complained of severe pain for one hour and 11 of moderate pain for half to one hour. The others found little discomfort after injection.

**Local reactions.** None was recorded.

**Systemic reactions.** Two patients complained of fever and giddiness a few hours after injection and this lasted for about 12 hours. One patient complained of chills and rigor five hours after injection, which was followed by fever for one day. This particular patient was known to be hypersensitive to penicillin. Another patient complained of generalised skin irritation for one week but there was no obvious rash.

**Blood counts and biochemical tests.** Blood counts, blood SGPT, and urea concentrations before and after treatment showed no significant change.

**Effect of concomitant medication.** Sixteen female patients were taking oral contraceptives, five male

prostitutes were taking oestrogen pills, and one male patient was taking antacids for gastric discomfort. All of them responded to treatment.

#### Discussion

The early cephalosporins were not very effective against *N gonorrhoeae*, but some of the newer ones, cephmandole, cefuroxime, and cefoxitin (cephamycin), are found to be effective against both PPNG and non-PPNG strains.<sup>8-10</sup> HR 756 is one of the second generation of cephalosporins which is highly effective against a wide variety of Gram-positive and Gram-negative bacteria, including *N gonorrhoeae*.<sup>11-13</sup>

In the present study, the clinical response was very good. The overall cure rate was 97.05% while that of PPNG and non-PPNG infections was 98.2% and 95.7% respectively. These results are totally acceptable epidemiologically. Bacteriologically, it was found that all the strains were inhibited by 0.3 µg/ml of the antibiotic. This is comparable to a previous study, in which 0.016 µg/ml of the antibiotic inhibited 68 strains of PPNG and 69 strains of non-PPNG.<sup>13</sup> It has been reported that higher concentrations of HR 756 are needed to inhibit non-PPNG strains, which were less susceptible to penicillin. This is confirmed in the present study, in which the MICs of HR 756 correlated directly with those of penicillin.

In-vitro studies indicated that HR 756 was more potent in inhibiting *N gonorrhoeae* than other antibiotics, such as tetracyclines, cefamandole, and cefoxitin.<sup>14</sup> The present in-vivo study seems to confirm this because of the good clinical response to only 500 mg of the drug in a single dose. The dosage of cefuroxime used by other workers was 2 g.<sup>9 10</sup>

TABLE IV Susceptibility of *N gonorrhoeae* to HR 756

Strains	Total	Minimum inhibitory concentration (µg/ml)							Mean MIC
		0.03	0.016	0.008	0.004	0.002	0.001	0.0005	
PPNG	16	1	6	5	1	3			0.011
Non-PPNG	52		4	14	10	3	7	14	0.0045

TABLE V Susceptibility of non-PPNG strains to HR 756 and penicillin G

MIC of HR 756 ( $\mu\text{g/ml}$ )	MIC of penicillin G ( $\mu\text{g/ml}$ )						
	2	1	0.5	0.25	0.125	0.062	0.031
0.016	3	1					
0.008	3	4	7				
0.004			3	5	2		
0.002			2	0	1		
0.001				1	2	4	
0.0005						9	5

TABLE VI Treatment failure according to susceptibility to HR 756

MIC ( $\mu\text{g/ml}$ )	No tested	Failure	
		No	%
0.004	38	0	0
0.008	19	2	10.5
0.016	11	1	9.1

None of the three patients who failed to respond to treatment carried strains which were resistant to the antibiotic; the MICs were 0.016, 0.008 and 0.008  $\mu\text{g/ml}$ . Correlation of the MICs with treatment response shows that failure may be expected with the present regimen when the MIC is 0.008  $\mu\text{g/ml}$  or above. Further studies will be necessary to determine if this is so.

The overall tolerance to the drug was good. It is interesting to note that one of the patients who had a systemic reaction was originally hypersensitive to penicillin. This illustrates the possibility of cross-sensitisation between penicillin and cephalosporins. The drug did not affect the blood counts and biochemical tests in any of the patients. The dose may be too small for non-allergic toxic reactions to appear.

We conclude that the antibiotic, HR 756, is effective and safe, especially at the relatively low dosage

of 500 mg. It is a good alternative to penicillin in the treatment of gonorrhoea because of its efficacy against the PPNG strains.

The authors thank Professor K E Chan and Mr William Ng of Hoechst (Singapore) Pte Ltd for the supply of drugs for use in this study.

## References

1. World Health Organisation. *Neisseria gonorrhoeae* and gonococcal infections. *Tech Report Series 616* Geneva: WHO, 1978;91-104.
2. Malverson CW, Clarke EJ. Single-dose treatment of gonorrhoea with selected antibiotic agents. *JAMA* 1969;210:857-65.
3. Brownlow WJ, Watko LP, Aucoin EJ, Iglecia-Fernandes R. Treatment of gonorrhoea contracted in the Western Pacific region. *Br J Vener Dis* 1974;50:113-7.
4. Rajan VS, Tan NJ, Tan T, Khoo R, Sng EH, Pang CP. Treatment of gonorrhoea: the Singapore experience. *Asian J Infect Dis* 1977;1:71-4.
5. Fu KP, Neu HC.  $\beta$ -lactamase stability of HR 756, a novel cephalosporin, compared to that of cefuroxime and cefoxitin. *Antimicrob Agents Chemother* 1978;14:322-6.
6. Martin JE, Armstrong JH, Smith PB. A new system for cultivation of *Neisseria gonorrhoeae*. *Appl Microbiol* 1974;27:802-5.
7. Catlin BW. Iodometric detection of *Haemophilus influenzae*  $\beta$ -lactamase; rapid presumptive test for dampicillin resistance. *Antimicrob Agents Chemother* 1975;7:265-9.
8. Arya OP, Rees E, Percival A, Alergant CD, Annels EH, Turner GC. Epidemiology and treatment of gonorrhoea caused by penicillinase-producing strains in Liverpool. *Br J Vener Dis* 1978;54:28-33.
9. Fowler W, Rahim G, Brown JD. Clinical experience in the use of cefuroxime in gonorrhoea. *Br J Vener Dis* 1978;54:400-4.
10. Price JD, Fluker JL. The efficacy of cefuroxime for the treatment of acute gonorrhoea in men. *Br J Vener Dis* 1978;54:165-9.
11. Neu HC, Aswapokee N, Aswapokee P, Fu KP. HR 756, a new cephalosporin active against Gram-positive and Gram-negative aerobic and anaerobic bacteria. *Antimicrob Agents Chemother* 1979;15:273-81.
12. Wise R, Rollason T, Logan M, Andrews JM, Bedford KA. HR 756, a highly active cephalosporin: comparison with cefazolin and carbenicillin. *Antimicrob Agents Chemother* 1978;14:807-11.
13. Tan RJS, Sng EH, Rajan VS, Lim AL, Yeo KL, Lim EW. Evaluation of cefotaxime (HR 756)—a new cephalosporin against penicillinase-producing strains of *Neisseria gonorrhoeae*. *Asian J Infect Dis* 1978;2:239-41.
14. Murray PR, Christman JL, Medoff G. In-vitro activity of HR 756, a new cephalosporin against *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 1979;15:452-4.